# Toxicology

**Lecture by:**

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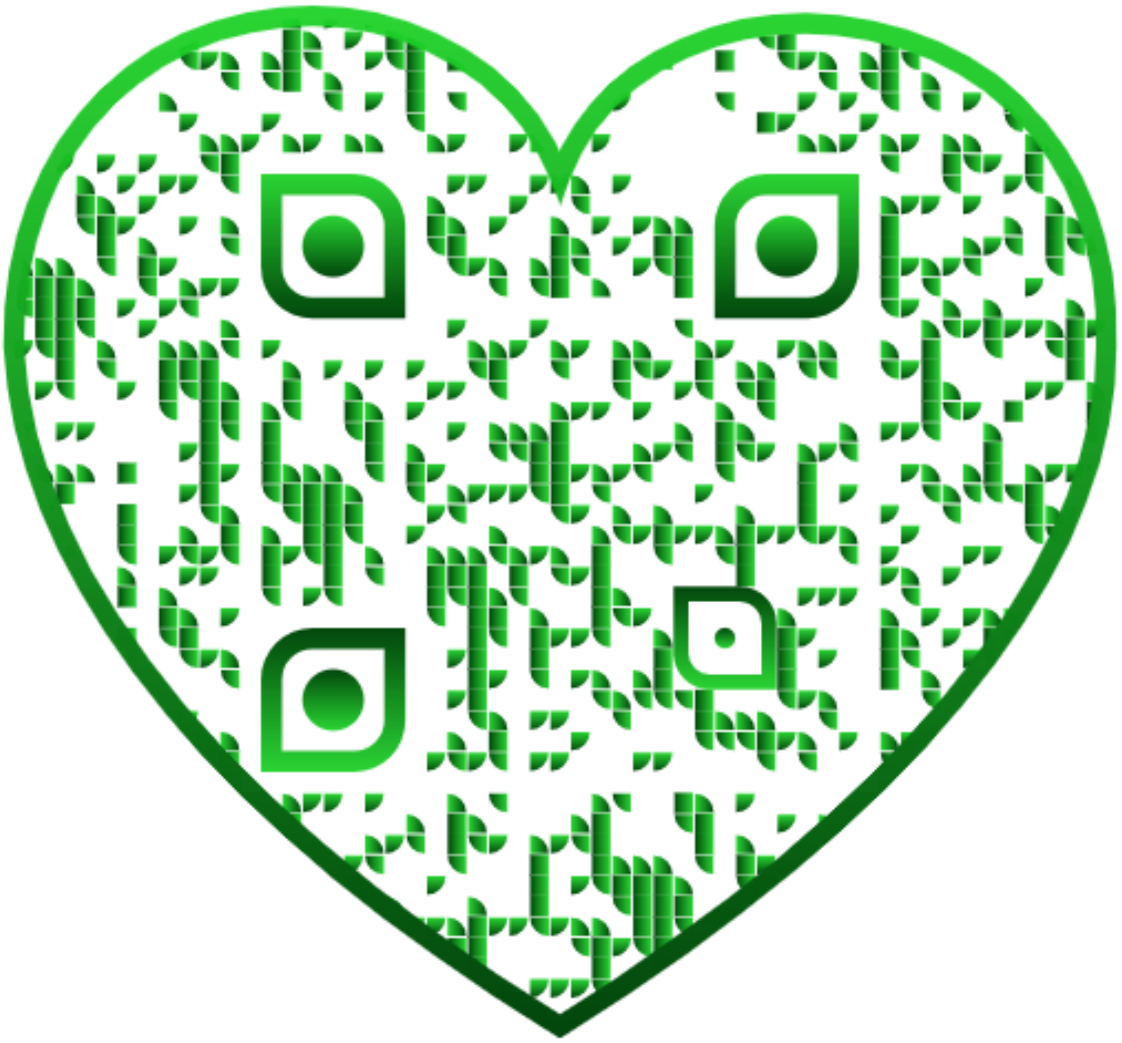


# Contents

- Definition of Toxicology and related terminologies
- Different areas of toxicology
- Major factors that influence toxicity
- Dose–Response Relationship
- Limitations DOSE-RESPONSE
- Variation in Toxic Responses
- Mechanisms of drug toxicity

# Objectives

- **At the end of this lecture the students will be able to:**
  - **To define toxicology and related terminologies**
  - **List the different branches of toxicology with their respective responsibility**
  - **Differentiate the difference between Toxicokinetics and Toxicodynamics**
  - **Discuss the steps and mechanism of drug toxicity**

# Definition of Toxicology

- It is derived from the Greek words - *toxicos* "poisonous" and *logos*- study.
  - Study of poisonous effect of drugs and other chemicals
- Deals with the " undesirable" /unwanted effects of or the adverse effects of chemical on living organisms….
  - It is both a science and an art (data gathering phase, predicting outcomes).
- It is the quantitative and qualitative study of the adverse effects of toxicants or physical agents on biological organisms.

# WHAT TOXICOLOGISTS DO?

- ✓ Involved in the recognition, identification, and quantification of hazard
- ✓ Develops standards and regulations to protect health and the environment
- ✓ Involved in safety assessment and use of data as basis for regulatory control of hazards
- ✓ Determines risk associated with use of chemicals
- ✓ Develop antidotes and treatment regimes
- The contributions and activities of toxicologists are diverse and widespread
- In the biomedical area
  - ➢ Toxicologists are concerned with mechanisms of action and exposure to chemical agents as a cause of acute and chronic illness
- In physiology and pharmacology
  - ➢ To understand physiological phenomena by using toxicants

# Definition of terminologies

- **Toxicity**- the ability of chemical agent to cause injury ( severity depends on dose).
- **Risk**- The measure or probability that a specific exposure situation or dose will produce a toxic effect.
- **Hazard**- The qualitative nature of the adverse or undesirable effect (i.e., the type of adverse effect) resulting from exposure to a particular toxicant or physical agent.
- **Dose** -The amount of a chemical that gains access to the body or the amount of chemical entering the body at a given time
- **Adverse effects**:
  - Any change from an organism's normal state or producing a *deleterious* effect.
  - Dependent upon the concentration of active compound at the target site for a sufficient time.

# Definition of terminologies…..

- **Exposure** – Contact providing opportunity of obtaining a poisonous dose.
- **Safety**- the probability that harm will not occur under specified conditions.
- **Toxin**: refers to toxic substances that are produced by biological systems such as plants, animals, fungi or bacteria Or it is poisons of biologic origin
- **Poisons** are chemicals with almost exclusively harmful effects
- **Toxicant:** is used in speaking of toxic substances that are produced by or are a by-product of anthropogenic (human-made) activities.
- *Any substance that causes a harmful (adverse) effect when in contact with a living organism at a sufficiently high concentration.*

# Definition of terminologies…..

| | |
|---|---|
| **Toxicants** | substances that produce adverse biological effects of any nature<br>may be chemical or physical in nature<br>effects may be of various types *(acute, chronic, etc.)* |
| **Toxins** | specific proteins produced by living organisms *(mushroom toxin or tetanus toxin)*<br>most exhibit immediate effects |
| **Poisons** | toxicants that cause immediate death or illness when experienced in very small amounts |

- **Xenobiotic :** Foreign substance taken in to the body(*xeno = foreign)*
- **Tolerance:** is a state of decreases responsiveness to a toxic effect of a chemical resulting from prior exposure to that chemical.

Two major mechanisms are responsible for tolerance:

✓Due to a decreased amount of toxicant reaching the site where the toxic effect is produced (dispositional tolerance)

✓Due to a reduced responsiveness of a tissue to the chemical.

# Different areas of toxicology

- The professional activities of toxicologist fall into four main branches or categories:

1. **Descriptive toxicology**
2. **Mechanistic toxicology**
3. **Regulatory toxicology**
4. Predictive toxicology

# Different areas of toxicology…

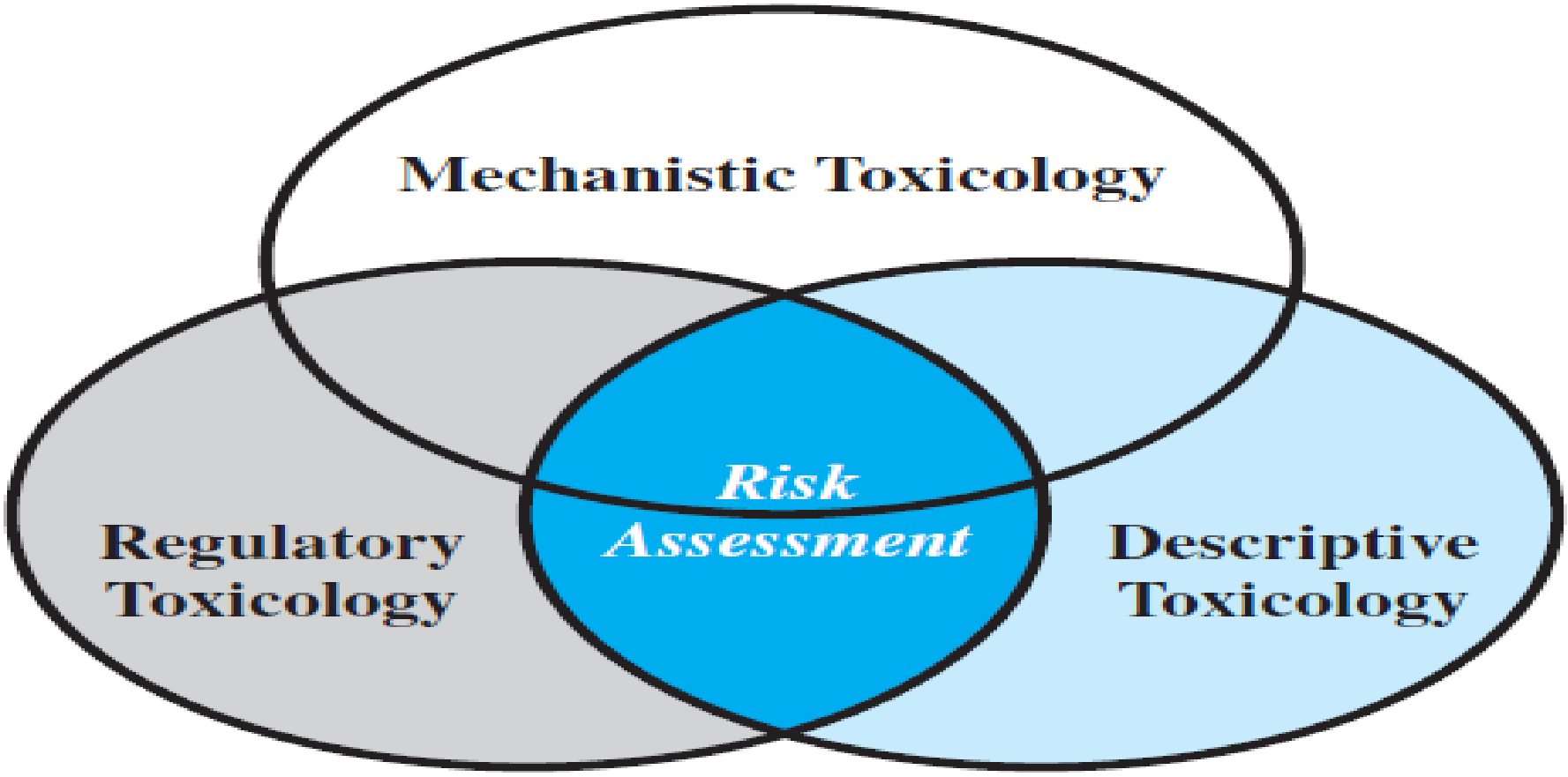



*Figure 2-1. Graphical representation of the interconnections between different areas of toxicology.*

# 1. Descriptive toxicology

- Concerned  directly with toxicity testing, which provides information for safety evaluation and regulatory requirements.
- Provide important clues to chemical mechanism of action (MOA)
  - Contribute to the development of mechanistic toxicology
- Key component of risk assessment that are used by regulatory toxicology

# 2. Mechanistic toxicology

- Is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms
- New technologies in molecular biology contributes to mechanistic toxicology
    - Tools to explore how humans may differ from lab. animals in their response to toxic effect substance
    - To identify and protect genetically susceptible individuals from harmful environmental exposures
    - To customize drug therapies that enhance efficacy and minimize toxicity based on their individual genetic makeup

# 2. Mechanistic toxicology….

- The results of mechanistic studies are very important in many areas of applied toxicology
- In risk assessment:

✓ Demonstrating an overdose outcome observed in lab animals is directly relevant to human

✓ Demonstrating adverse response that may not be relevant to human

✓ Design and production of safer alternative chemical in rational therapy for chemical poisoning and treatment of disease

# 2. Mechanistic toxicology….

- In risk assessment:
  - ➢The process by which the potential (or probability of) adverse health effects of exposure are characterized.
  - –*Steps:*
    - –Toxicity determination
    - –Toxicity evaluation
    - –Hazard assessment
    - –Risk estimation
    - –Risk evaluation

# 3. Regulatory toxicology

- Responsibility for deciding whether a drug or another chemical poses a sufficiently low risk to be marketed for a stated purpose
  - *On the basis of data provided by descriptive and mechanistic toxicologists*

- Establishment of standards for the amount of chemicals permitted in ambient air, industrial atmospheres, and drinking water
- Allow use/ sales of drugs, cosmetics, food, and other chemicals

# 4. Predictive toxicology

- Studies about the potential and actual risks of chemicals.
- This is important for licensing a new drug/ chemical for use.

# Specialized areas of toxicology

- ✓ **Forensic toxicology**: A hybrid of analytic chemistry and fundamental toxicological principles. medicolegal aspects of the harmful effects of chemicals on man (aid in establishing the cause of death in a postmortem investigation)
  - For instance, where there is a suspicion of murder, attempted murder or suicide by poisoning.
  - **Clinical toxicology**: concerned with disease caused by or uniquely associated with toxic substances ( e.g. poison management)
  - **Occupational toxicology:** Deals with chemical found in the workplace.
  - **Environmental toxicology**: focuses on the impacts of chemical pollutants in the environment on biological organisms.
  - **Ecotoxicology** *:*is a specialized area within environmental toxicology that focuses more specifically on the impacts of toxic substances on population dynamics in an ecosystem

# Major factors that influence toxicity

- **Route of exposure**
- **Duration and frequency of exposure**
  - Acute: < 24hour, usually single exposure
  - Sub acute: ≤ 1month, repeated doses
  - Sub chronic: 1-3months, repeated doses
  - Chronic : > 3 months, repeated doses
  - For many agents, the toxic effects that follow a single exposure are quite different from those produced by repeated exposure
    - E.g. Benzene- acute exposure causes CNS depression while chronic exposure manifests as bone marrow depression
- **Dose/ concentration**

# Major factors…

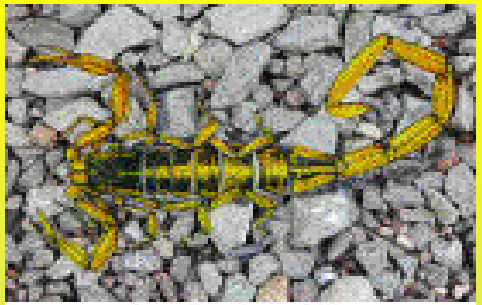
## Route of Exposure

- The **route** (site) of exposure is an important determinant of the ultimate **dose**—different routes may result in different rates of absorption.
  - Dermal (skin)
  - Inhalation (lung)
  - Oral ingestion (Gastrointestinal)
  - Injection
- The route of exposure may be important if there are tissue-specific toxic responses.
- Toxic effects may be local or systemic

# Major factors…

- Duration and frequency of exposure
- **Acute toxicity**
  - occurs almost immediatly (hr / day) after exposure
  - Usually single dose at large dose
- **Subchronic toxicity**
  - Results from repeated exposure for several weeks or months
- **Chronic toxicity**
  - Represents cumulative damage to specific organ system and takes many months or years to become a recognizible clinical disease
  - Ex : cirrhosis in alcoholics, chronis bronchitis in long-term cigarrete smokers, pulmonary fibrosis in coal

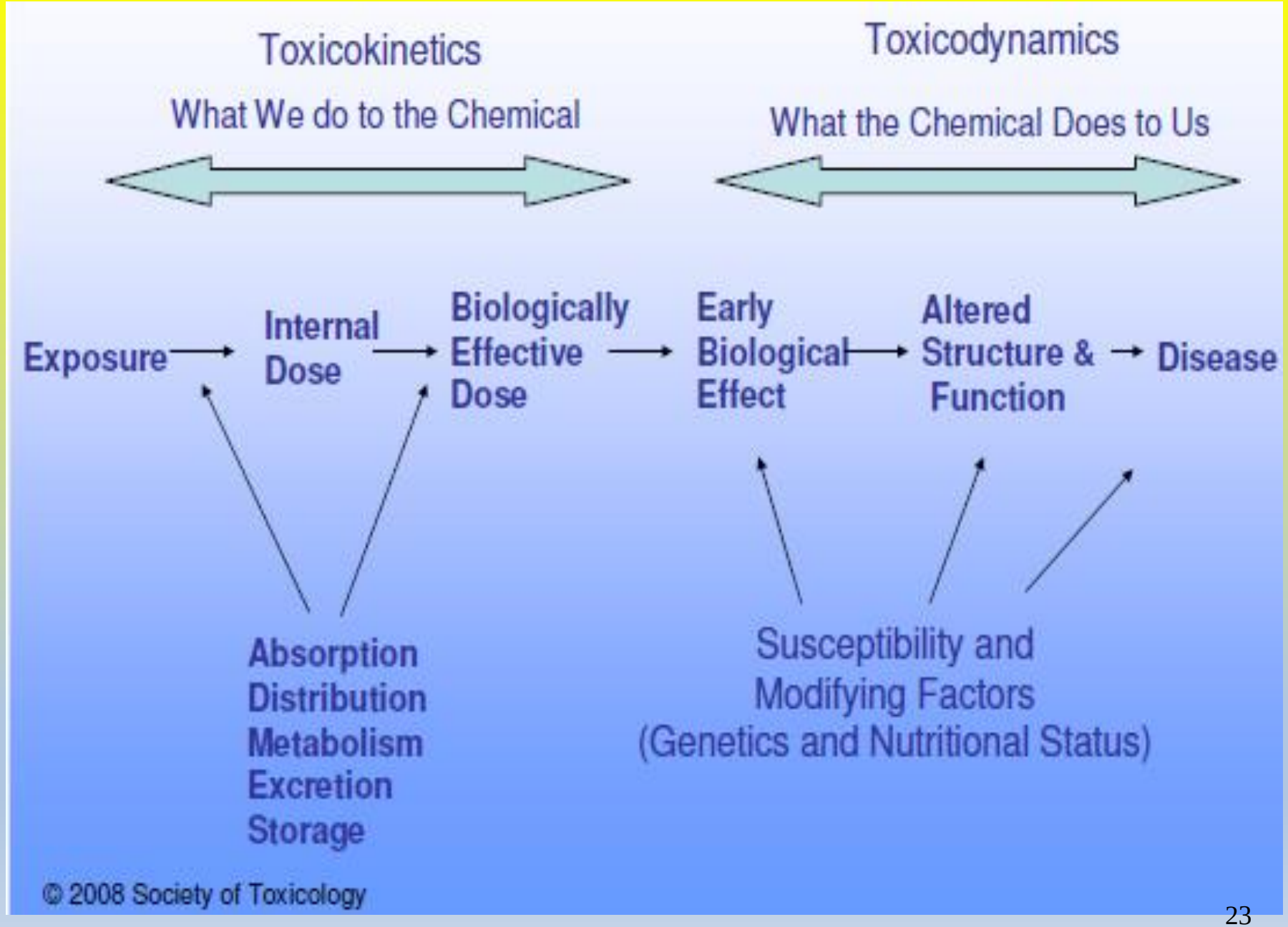
– *Exposure to chemicals may come from many sources*
  - Environmental
  - Occupational
  - Therapeutic
  - Dietary
  - Accidental
  - Deliberate



# Toxicokinetics

- Absorption
- Distribution
- Metabolism
- Excretion

| | |
|---|---|
| **Absorption** | The substance enters the body. |
| **Distribution** | The substance moves from the site of entry to other areas of the body. |
| **Biotransformation** | The body changes *(transforms)* the substance into new chemicals *(metabolites)*. |
| **Excretion** | The substance or its metabolites leave the body. |


Toxicokinetics
What We do to the Chemical
Toxicodynamics
What the Chemical Does to Us
Exposure
Internal Dose
Biologically Effective Dose
Early Biological Effect
Altered Structure & Function
Disease
Absorption
Distribution
Metabolism
Excretion
Storage
Susceptibility and Modifying Factors
(Genetics and Nutritional Status)
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# Absorption

- Inhalation: readily absorb gases into the blood stream via the alveoli.
  - (Large alveolar surface, high blood flow, and proximity of blood to alveolar air)
- Ingestion: absorption through GI tract stomach (acids), small intestine (long contact time, large surface area
- Dermal: absorption through epidermis (stratum corneum), then dermis; site and condition of skin

# Distribution

- Process whereby an absorbed chemical move away from the site of absorption to other areas of the body.
- Blood carries the agent to and from its site of action, storage depots, organs of transformation, and organs of elimination
- Rate of distribution (rapid) dependent upon
  - Blood flow
  - Characteristics of toxicant (affinity for the tissue, and the partition coefficient)

# Distribution also affected by

- Porosity of capillaries
- Specialized membrane transport
- Accumulation in cell organelles
- Reversible intracellular binding
- Plasma protein binding
- Specialized barriers

- E.g.
  - Na, K ATPase promotes intracellular accumulation of thallous ion and voltage-gated $Ca^{++}$ channels permit the entry of cations such as lead or barium ions into excitable cells

# Metabolism

- Process whereby a substance is changed from one chemical to another by a chemical reaction in the body.
- The main aim to make chemical agents more water soluble and easier to excrete
  - Decrease lipid solubility --> decrease amount at target
  - Increase ionization --> increase excretion rate --> decrease toxicity
- Biotransformation occurs in the Liver, kidney, lung, gastrointestinal track, and other organs
  - Bioactivation--Biotransformation can result in the formation of reactive metabolites

| Drug | Drug Category | Metabolic Defect | Toxic Effect |
|---|---|---|---|
| Isoniazid | antituberculosis drug | slow acetylation | nerve and liver damage |
| Hydralazine | antihypertensive drug | defect in mono-oxygenase enzyme | excessive fall in blood pressure |
| Dapsone | antibacterial agent | slow acetylation | systemic lupus erythematosus |
| Primaquine | antimalarial agent | defective G6PD | acute hemolytic anemia |

# Excretion

- Urinary excretion
  - water soluble products are filtered out of the blood by the kidney and excreted into the urine
- Exhalation
  - Volatile compounds are exhaled by breathing
- Biliary Excretion via Fecal Excretion
  - Compounds can be extracted by the liver and excreted into the bile.
  - The bile drains into the small intestine and is eliminated in the feces.
- Milk, Sweat, Saliva

# Toxicodynamics (TD)

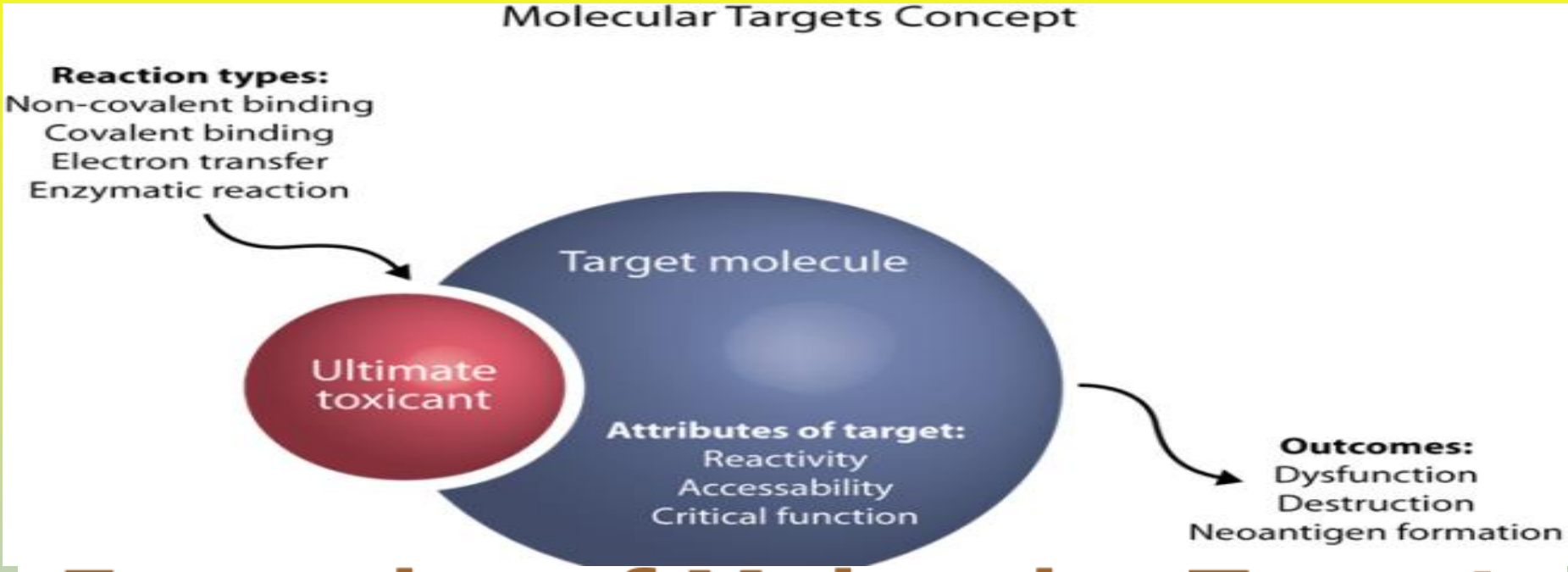
- Toxicodynamics is concerned with processes and changes that occur to the toxicants at the target tissue, including metabolism and binding that results in an adverse effect.
- TD can be defined as what a toxicant does on the body (mechanism of action)

- **Toxicodynamics** (Determines the no. of receptors that can interact with toxicants)
  - Binding
  - Interaction
  - Induction of toxic effects

# Toxicodynamics (TD)…

- It also defined as the molecular, biochemical, and physiological effects of toxicants or their metabolites in biological systems.
- These effects are result of the interaction of the biologically effective dose of the ultimate (active) form of the toxicant with a molecular target.

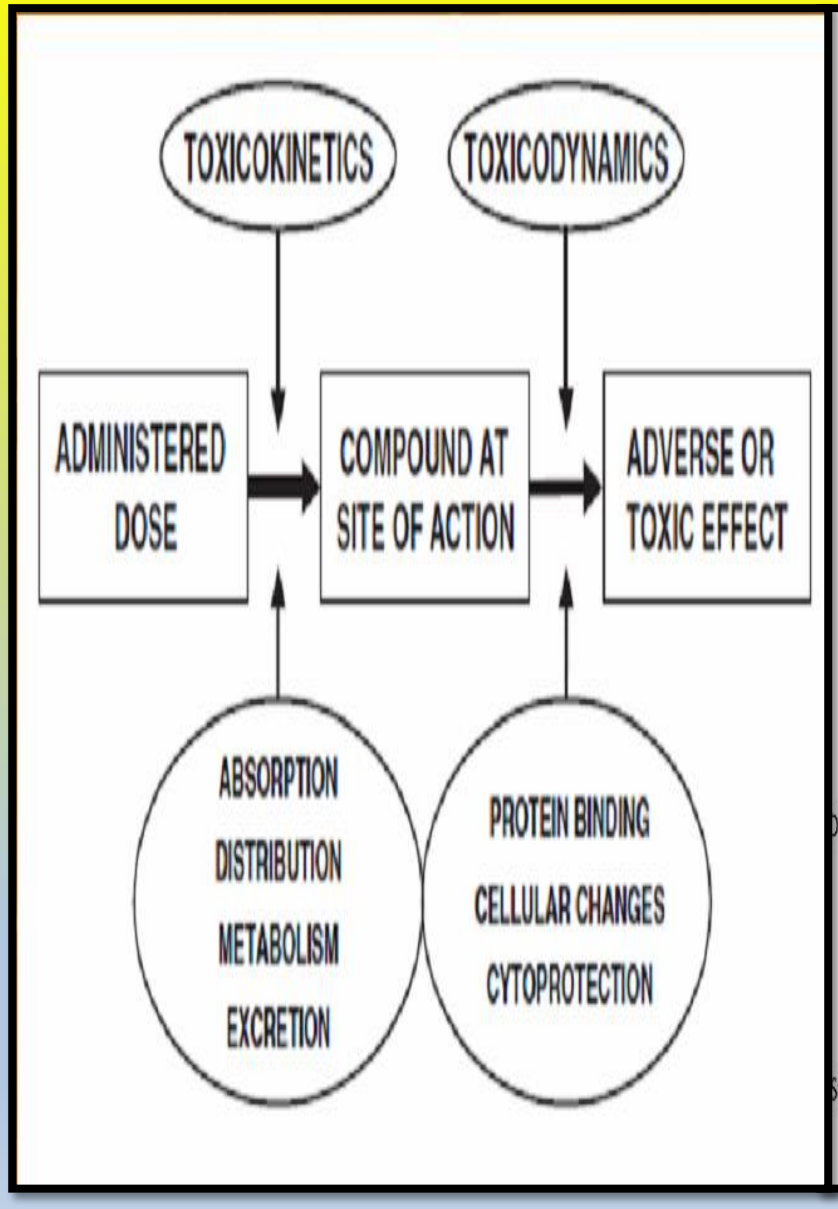
# Toxicodynamics (TD)…

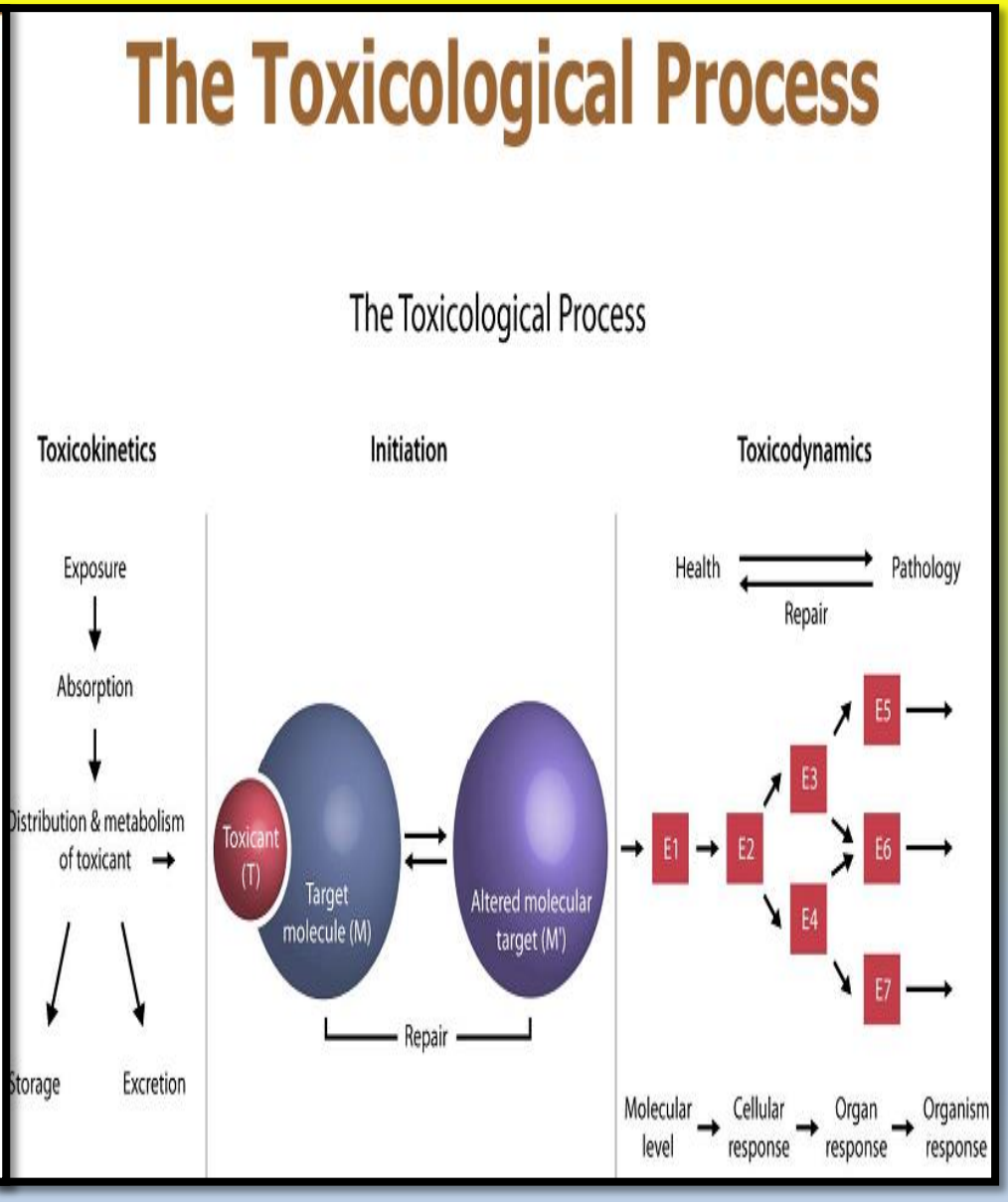



## Examples of Molecular Targets

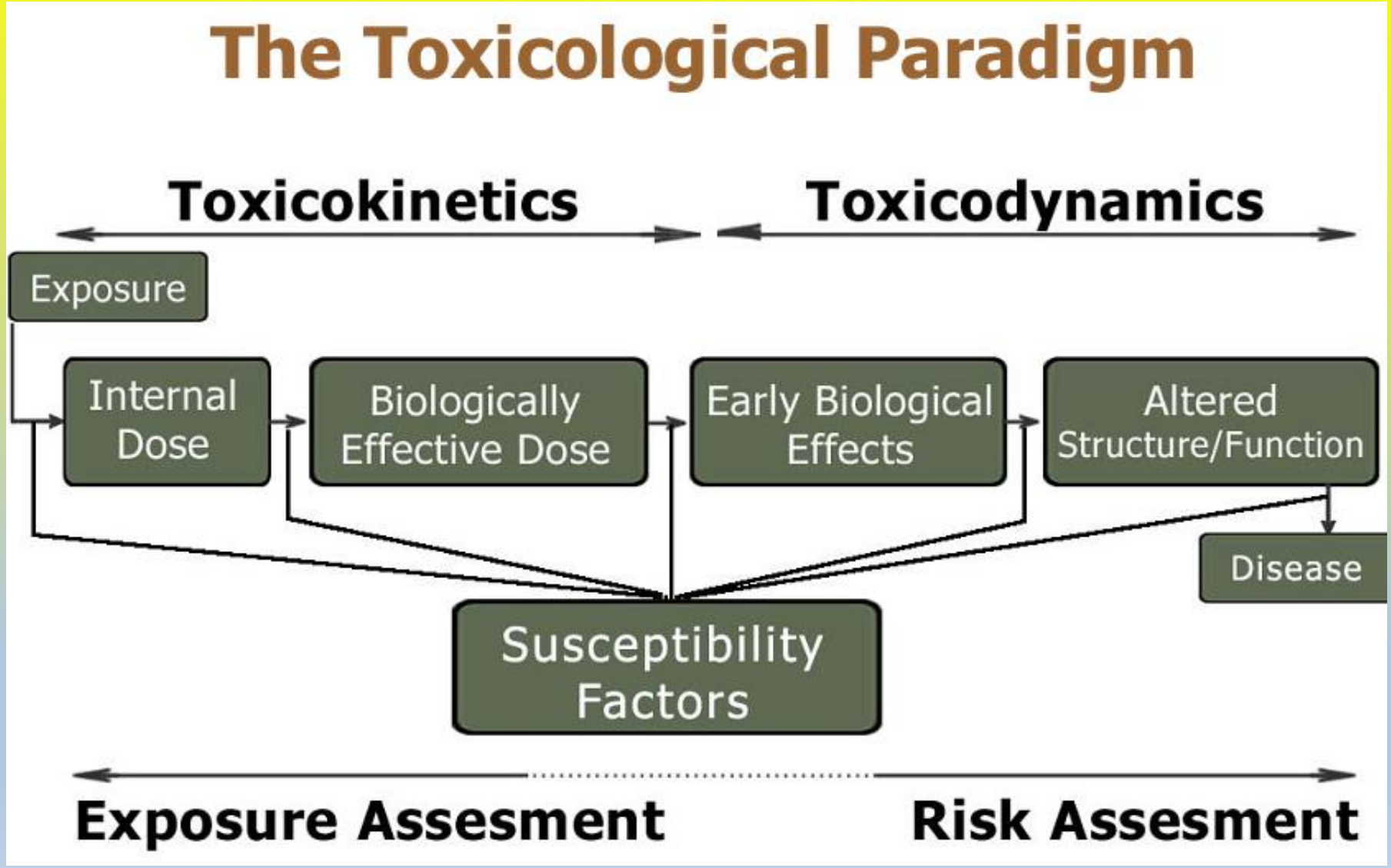
- Proteins
  - **A**ryl**h**ydrocarbon(Ah) receptor—Dioxin
  - Hemoglobin—CO
- Lipids—Carbon tetrachloride
- DNA—Aflatoxin

# Toxicodynamics (TD)…



# Toxicodynamics (TD)…



# Variation in Toxic Responses

# Variation in Toxic Responses

- **Selective Toxicity:**
  - a chemical produces injury to one kind of living matter without harming another form of life.
    - ✓**biological diversity**
    - ✓interferes with the ability of ecotoxicologists to predict the toxic effects of a chemical in one species from experiments performed in another species.
    - ✓However, by taking advantage of the biological diversity,
      - ➢ It is possible to develop chemicals that are lethal for an undesired species and harmless for other species.

# Variation in Toxic Responses

- **Selective Toxicity:**
  - Drugs and other chemicals used for selective toxic purposes are selective for one of two reasons.

1. *The chemical is equally toxic to both **desirable** and undesirable cells but is accumulated mainly by **undesirable** cells,*
   - ✓ The effectiveness of **radioactive iodine** in the treatment of hyperthyroidism as well as its thyroid carcinogenicity
   - ✓ due to the selective ability of the **thyroid gland** to accumulate iodine.

# Variation in Toxic Responses

- **Selective Toxicity:**

2. *It reacts fairly specifically with a cytological or a biochemical feature that is absent from or does not play an important role in the desired form.*

  - ✓bacteria contain cell walls but not humans
  - ✓This has been utilized in developing selective toxic chemotherapeutic agents,
    - ➢**Penicillins**, **cephalosporins**

# Variation in Toxic Responses

- **Species (strain) Differences:**
  - ***Penicillin*** *is fatal for guinea pigs but generally well tolerated by humans*
  - ***Aspirin*** *is teratogenic in cats, dogs, rats, and mice but not in pregnant women*
  - ***Thalidomide*** *doesn't cause birth defects in rats or many other species.*

# Variation in Toxic Responses

- Species (strain) Differences:
  - There are anatomical, physiological, and biochemical differences among animal species.
  - For instance, Rat differs substantially from humans:
    - ✓*it lacks gall bladder*
    - ✓*Displays less efficient plasma binding*
    - ✓*An obligate nose breather*
    - ✓*Has different location of gut flora, etc*

# Variation in Toxic Responses

- This problem of species-specific responses to chemicals creates somewhat of a paradox in toxicological research.
- The goal of the toxicologist's study is the prediction of chemical effects on humans by using animal studies.
- However, selection of the right animal for that study requires a prior knowledge of the fate and effects of the chemical in humans, as well as its fate and effects in various animals.

# Variation in Toxic Responses

- **Individual Differences:**
  - **– Genetic make up**
    - ✓**G6PD**
      - ➢ people deficient are more susceptible than others to the hemolysis of blood by **aspirin** or certain antibiotics,
    - ✓**p53 gene, tumor suppressor gene**
      - ➢ mice possessing mutated p53 are much more susceptible to some chemical carcinogens than are mice with normal copies of the gene.
    - ✓slow acetylators are more susceptible to neuropathy and hepatotoxicity from ***isoniazid***.

# Variation in Toxic Responses

- **Individual Differences:**
  - **SEX**:
    - ✓**male** animals of many rodent strains have a significantly greater capacity for the liver metabolism and breakdown of chemicals
      - ➢they have more **CYP450**.
      - ➢cause the male animals of certain rodent strains to be ***more or less susceptible*** to toxicity from a chemical
        - » depending on whether oxidative metabolism represents a **bioactivation** or **detoxification** pathway.

# Variation in Toxic Responses

- **Individual Differences:**
  - **SEX**:
    - ✓**strychnine**
      - ➢ is less toxic to **male** rats when administered orally
      - ➢ This allows them to survive a dose that is lethal to their female counterparts.
    - ✓For chemicals that are bioactivated to a toxic, reactive intermediate,
      - ➢**male** rodents more susceptible to the liver toxicity and carcinogenicity.

# Variation in Toxic Responses

- **Individual Differences:**
  - ***Age: geriatrics and pediatrics***
    - The acute **LD50** dose of chloroform is **446 mg/kg** in ***14-day-old Sprague–Dawley rats***, but
    - this dose increases to **1188 mg/kg** in the **adult** animal.

# Variation in Toxic Responses

- ***Effects of Chemical Interaction***
  - Synergism,
  - Potentiation
  - Antagonism
- ***Route of Exposure***
  - The exposure pathway by which a substance comes in contact with the body determines
    - how much of it enters (rate and extent of absorption) and
    - which organs are initially exposed to the largest concentration of the substance.

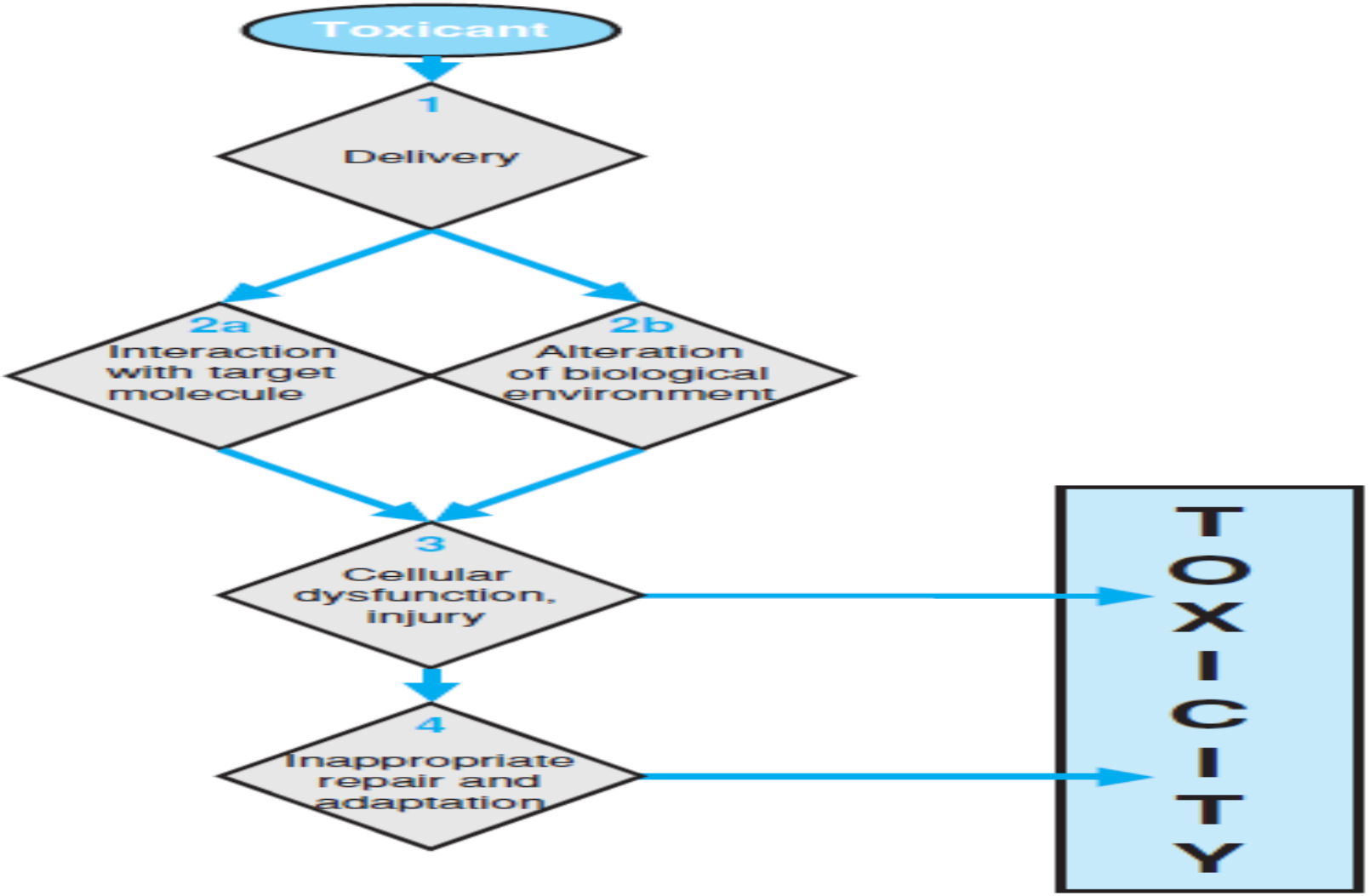
# Drug Toxicity

- All drugs have both primary intended effects and secondary unintended effects (side effects or adverse effects).
- Adverse effects range in severity from nuisance to life threatening
- The occurrence and/or severity of Adverse effects depends on many factors (dose, age, preexisting condition, genetic make-up, etc).

# Mechanisms of drug toxicity

Toxicant delivery to site of action

- The intensity of a toxicity depends on the concentration and persistence of the toxicant at its site of action
- The target concentration of the toxicant depends on
  - Absorption, distribution, reabsorption, activation, deactivation, presystemic elimination, etc




**Potential stages in the development of toxicity after chemical exposure**

# Mechanisms of Toxicity

- Path to toxicity involves many steps
  - First, the toxicant is delivered to its target or targets
    - **Step 1**
  - Then the ultimate toxicant interacts with endogenous target molecules
    - **Step 2**
  - Triggering perturbations in cell function and/or structure
    - **Step 3**

# Mechanisms of Toxicity

- Path to toxicity…
  - ✓ This initiate,
    - – Repair mechanisms at the molecular, cellular, and/or tissue levels as well as
    - – Adaptive mechanisms to diminish delivery, boost repair capacity and/or compensate for dysfunction
      - ➢ **Step 4**

# Mechanisms…

- Path to toxicity…
  - When the perturbations induced by the toxicant exceed repair and adaptive capacity, or
  - when repair and adaptation becomes malfunctional,

➢Toxicity!!!

# Mechanisms…

- Sometimes a xenobiotic *does not* react with a specific target molecule but rather adversely influences the *biological environment*, causing
  - ✓molecular
  - ✓organellar
  - ✓cellular, or
  - ✓organ dysfunction leading to deleterious effects.

# Mechanisms…

- 2,4-dinitrophenol,
  - ✓after entering the mitochondrial matrix space
    - ➢**step 1**
  - ✓collapses the outwardly directed proton gradient across the inner membrane by its mere presence there
    - ➢**step 2**
  - ✓causing mitochondrial dysfunction which is manifest in toxic effects such as hyperthermia and seizures.
    - ➢**step 3**

# Mechanisms…

- Step 1:- **Delivery**
  - Theoretically, the intensity of a toxic effect depends primarily on
    - ✓the concentration and
    - ✓persistence of the ultimate toxicant at its site of action.
  - The ultimate toxicant is the chemical species
    - ✓that reacts with the endogenous target molecule or
    - ✓critically alters the biological environment

# Mechanisms…

- Step 1:
  - Often the ultimate toxicant is the original chemical to which the organism is exposed.
    - ✓*Methylisocyanate, HCN, CO*
  - In other cases, the ultimate toxicant is
    - ✓a metabolite of the parent compound or
    - ✓a reactive oxygen or nitrogen species generated during the biotransformation of the toxicant.
      - ➢Acetaminophen → N-Acetyl-p-benzoquinoneimine
      - ➢*CCl4 → CCl3OO•*

# Mechanisms…

- Step 1:
  - The concentration of the ultimate toxicant at the target molecule depends on the relative effectiveness of the processes that
    - ✓ *increase* or
    - ✓ *decrease* it's concentration at the target site

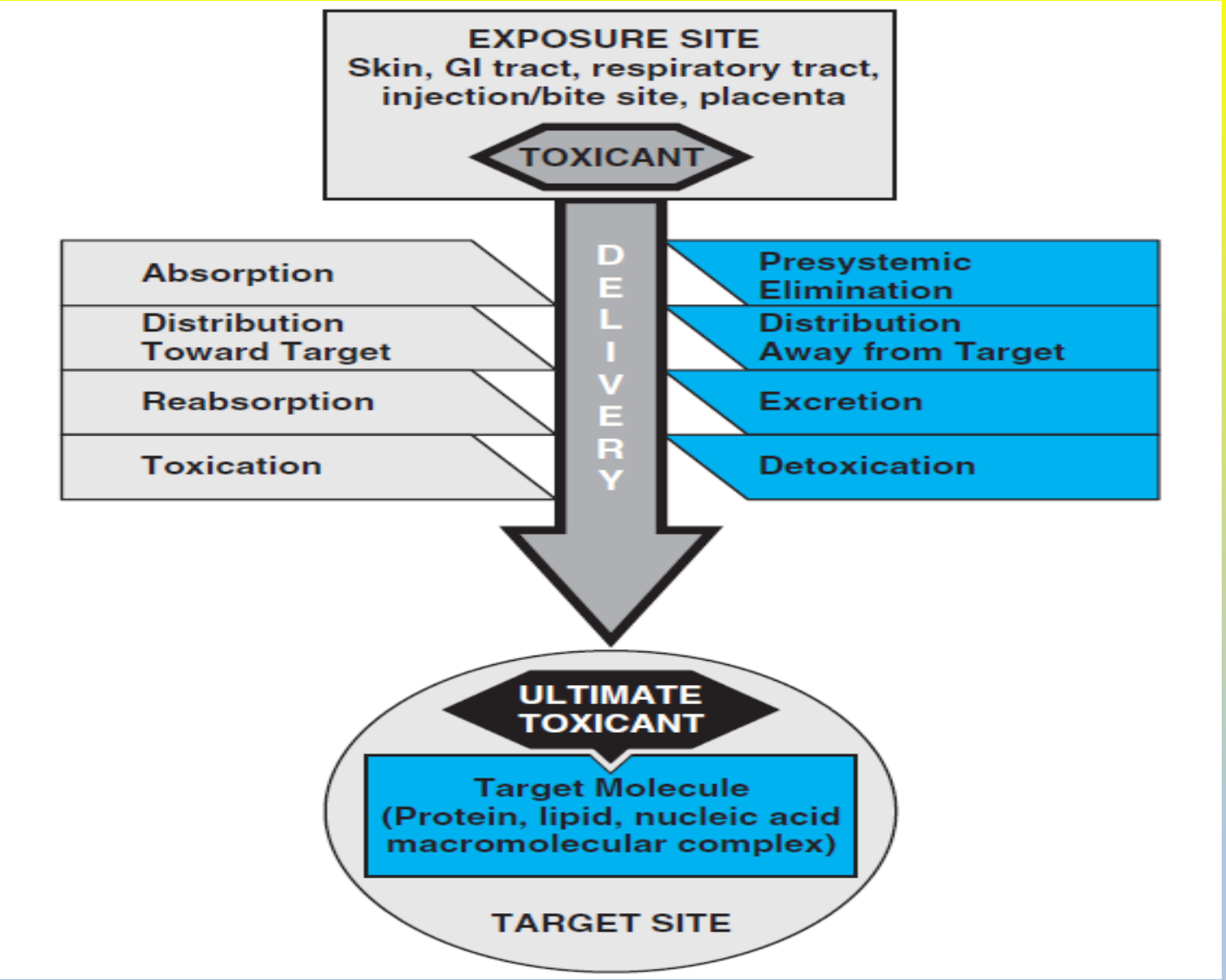
.

# Mechanisms…

- Step 1:
  - The accumulation of the ultimate toxicant at its target is facilitated by its
    - ✓absorption,
    - ✓distribution to the site of action,
    - ✓reabsorption, and
    - ✓toxication (metabolic activation).

# Mechanisms…

- Step 1:
  - Conversely, the following work against the accumulation of the ultimate toxicant at the target molecule
    - ✓presystemic elimination,
    - ✓distribution away from the site of action,
    - ✓excretion, and
    - ✓detoxication



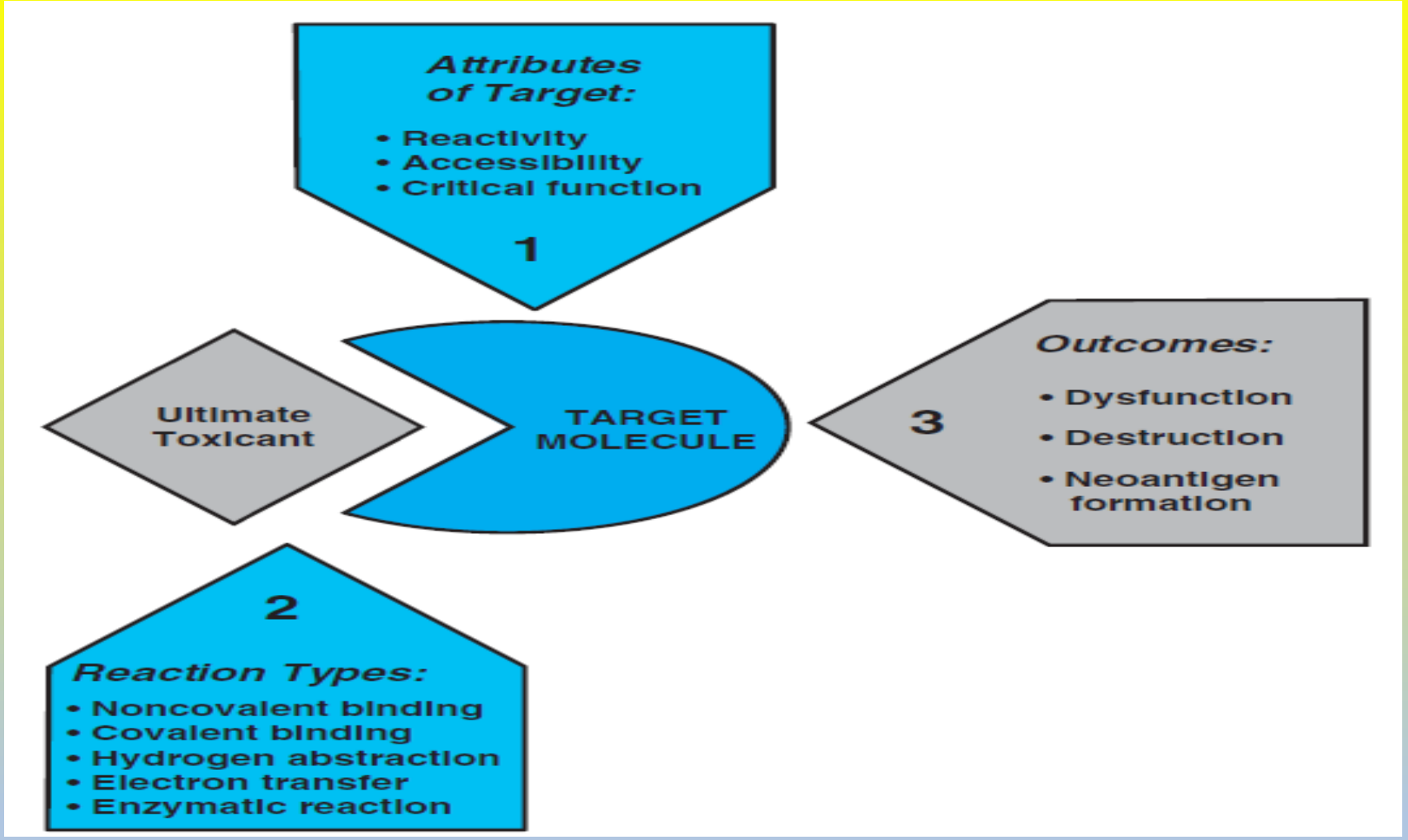

**The process of toxicant delivery is the first step in the development of toxicity**

# Mechanisms…

- Step 2: **Reaction of the Ultimate Toxicant with the Target Molecule**
  - a series of secondary biochemical events occur, leading to dysfunction or injury that is manifest at various levels of biological organization,
    - ✓at the target molecule itself,
    - ✓cell organelles & cells,
    - ✓tissues and organs, and even the whole organism.

# Mechanisms…

- Step 2:
  - Because interaction of the ultimate toxicant with the target molecule triggers the toxic effect, consideration is given to
    1. ***the attributes of target molecules,***
    2. ***the types of reactions between ultimate toxicants and target molecules, and***
    3. ***the effects of toxicants on the target molecules .***




**Reaction of the ultimate toxicant with the target molecule: the second step in the development of toxicity.**

# Mechanisms…

- Step 3: **Cellular Dysfunction and Resultant Toxicities**
  - Each cell in a multi-cellular organism carries out defined programs.
    - Certain programs determine the destiny of cells i.e,
      - ✓ whether they undergo division,
      - ✓ differentiation (express proteins for specialized functions), or
      - ✓ apoptosis.

# Mechanisms…

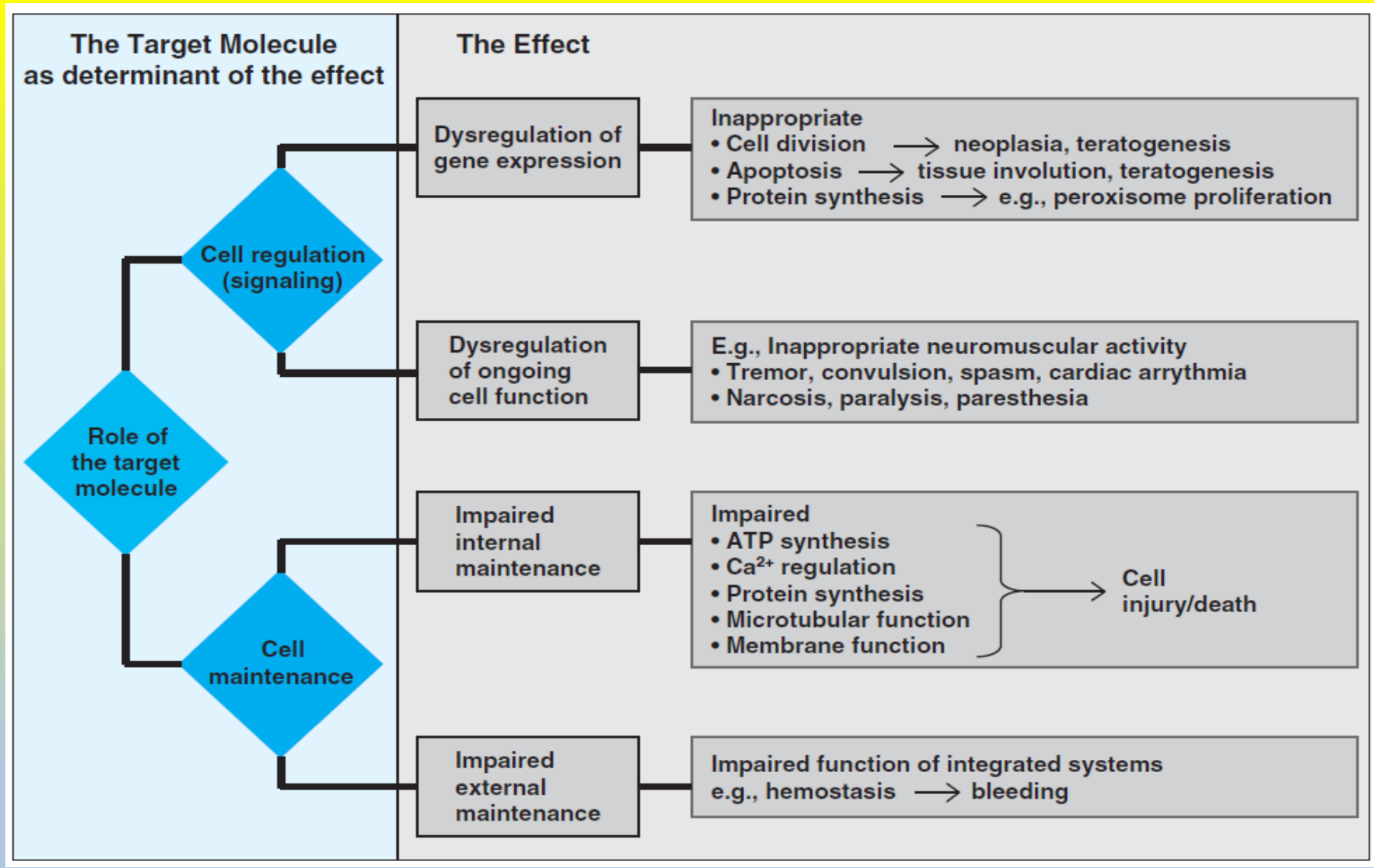
- Step 3:
  - Other programs control the ongoing activity of differentiated cells determining whether they
    - *secrete more or less of a substance*
    - *contract or relax, and*
    - *transport and metabolize nutrients at higher or lower rates.*

# Mechanisms…

- Step 3:
  - The nature of the primary cellular dysfunction caused by toxicants, but not necessarily the ultimate outcome, depends on the role of the target molecule affected.
    - ✓If the target molecule is involved in cellular regulation,
      - ➢dysregulation of gene expression, and/or dysregulation of momentary cellular function occurs primarily.

# Mechanisms…

- Step 3:
  - However, if the target molecule is involved predominantly in the cell's internal maintenance,
    - ✓the resultant dysfunction can ultimately compromise the survival of the cell.
  - The reaction of a toxicant with targets serving external functions can influence the operation of other cells and integrated organ systems.




**The third step in the development of toxicity: alteration of the regulatory or maintenance function of the cell.**

# Mechanisms…

- Step 4: **Inappropriate Repair and Adaptation**
  - Many toxicants alter macromolecules, which eventually cause damage at higher levels of the biological hierarchy in the organism.
  - Progression of toxic lesions can be intercepted by repair mechanisms operating at molecular, cellular, and tissue levels
  - Another strategy whereby the organism can resist the noxious chemical is by increasing its own readiness to cope with it and with its harmful effects.
    - ✓Adaptation

# *Factors influencing toxicity*

❖Many factors affect the reaction of an organism to a toxic chemical.

- ✓ **Form and innate chemical activity**
- ✓ **Dosage, especially dose-time relationship**
- ✓ **Exposure route**
- ✓ **Species**
- ✓ **Age**
- ✓ **Sex**

- ✓ **Ability to be absorbed**
- ✓ **Metabolizme**
- ✓ **Distribution within the body**
- ✓ **Excretion**
- ✓ **Presence of other chemicals**

## Form

Examples : - methyl mercury – mercury vapour (element)

- $Cr^{3+}$ - $Cr^{6+}$ (Hexavalent salts are regarded as the most hazardous ones)

## Innate

Examples : HCN ⟶ cytohrome oxidase ⟶ hypoxia

Nicotine ⟶ cholinergic receptor ⟶ paralysis

## Dosage

| **Toxicant** : | **Acute toxicity** : | **Chronic toxicity** : |
|---|---|---|
| Ethanol | CNS depressant | liver cirrhosis |
| Arsenic | GIT damage | skin / liver damage |

## Route of Exposure :

- Ingested chemicals : intestine → liver → distributed
- Inhaled chemicals : blood circulation → whole body
- Liver : the most active organ for chemicals → inactivation

- Hepatotoxicity
  - Toxicity to the liver, bile duct and gall bladder

| | |
|---|---|
| **Steatosis** | lipid accumulation in hepatocytes |
| **Chemical hepatitis** | inflammation of the liver |
| **Hepatic necrosis** | death of the hepatocytes |
| **Intrahepatic cholestasis** | backup of bile salts into the liver cells |
| **Hepatic cancer** | cancer of the liver |
| **Cirrhosis** | chronic fibrosis, often due to alcohol |
| **Hypersensitivity** | immune reaction resulting in hepatic necrosis |

# Selective toxicity :

Differences in toxicity between two species

- Antibiotics lethal for microorganisme, nontoxic to human.
- An insectcide is lethal to insect, not to human.

**Age** :

- parathion is more toxic to young animals
- nitrosamines are more carcinogenis to new born or young animals

**Sex** :

- male rats 10 x more sensitive to liver damage from DDT
- female rats 2x more sensitive to parathion
- Alcohol intoxication (male Vs female)?

**Ability to be absorbed :**

- ethanol is readily absorbed from GIT but poorly absorbed through the skin

- organic mercury is readily absorbed from GIT, but inorganic mercury is not

Metabolism = biotransformation

Is a major factor in determining toxicity

- detoxification (bioinactivation) : process b y which a xenobiotic is converted to a less toxic form ⟶ water soluble

- bioactivation : process by which a xnobiotic may be converted to more reactive or toxic form.

Distribution :

Determine the sites where toxicity occur.

Depend on how the lipid-solubility

# INTERACTION

## Type of interaction :

| | |
|---|---|
| **additivity** | a combination of two or more chemicals is the sum of the expected individual responses |
| **antagonism** | exposure to one chemical results in a reduction in the effect of the other chemical |
| **potentiation** | exposure to one chemical results in the other chemical producing an effect greater than if given alone |
| **synergism** | exposure to one chemical causes a dramatic increase in the effect of another chemical |

The interactions described can be categorized by their chemical or biological mechanisms as follows:

- chemical reactions between chemicals
- modifications in absorption, metabolism, or excretion
- reactions at binding sites and receptors
- physiological changes

## Additive :

Tranquilizer + alcohol

Two Organophosphate

Organochlorine + halogenated solvent

## Synergism :

Cigaret smoke + radon ($_{86}Rn$)

Ethanol + carbontetrachloride

## Potentiation :

Carbontetrachloride (hepatotoxic) + isopropanol

## Antagonism

Chemicals/drugs and their antagonist

**Antagonism :** Effect of one chemical is diminished or completely abolished in the presence of another.

| | |
|---|---|
| **physiological antagonism** | a severe drop in blood pressure resulting from a barbiturate overdose can be reversed by administration of a vasopressor to increase blood pressure |
| **chemical antagonism** | mercury toxicity can be reduced by chelating *(binding)* the mercury ions with dimercaprol |
| **disposition antagonism** | swallowed poison is absorbed by introducing charcoal into the stomach |
| **receptor antagonism** | carbon monoxide poisoning is treated with oxygen which displaces the carbon monoxide from hemoglobin receptors |

# Toxication

- It refers Biotransformation to harmful products
  - ✓ *It is also known as* *metabolic activation*
- *Physicochemical: E.g.* oxalic acid formed from ethylene glycol may cause acidosis and hypocalcaemia as well as obstruction of renal tubules by precipitation as calcium oxalate
- *Increased reactivity:* could be due to conversion into: Electrophiles, Free radicals, Nucleophiles or Redox-active reactants

# Toxication……

- **Nucleophiles** generally are detoxicated by conjugation at the nucleophilic functional group
- **Electrophiles** are molecules containing an electron-deficient atom with a partial or full positive charge that allows it to react by sharing electron pairs with electron-rich atoms in nucleophiles
- **A free radical** is a molecule or molecular fragment that contains one or more unpaired electrons in its outer orbital.
- Radicals are formed by

(1) accepting an electron(paraquat, doxorubicin, and nitrofurantoin)

(2) losing an electron (phenols, hydroquinones, aminophenols, amines)

(3) homolytic fission of a covalent bond(CCl4 to the trichloromethyl free radical (Cl3C•)

# Detoxication

- It refers to biotransformation that eliminate the ultimate toxicant or prevent its formation.
- Detoxication may be insufficient for several reasons:
  - Toxicants may overwhelm detoxication processes
  - A reactive toxicant inactivates a detoxicating enzyme
  - Some conjugation reactions can be reversed

❑ Detoxication can take several pathways, depending on the chemical nature of the toxic substance

- *Detoxication of Nucleophiles*
  - Nucleophiles generally are detoxicated by conjugation at the nucleophilic functional group

# Detoxication

- ***Detoxication of electrophiles***
  - A general mechanism for the detoxication of electrophilic toxicants is conjugation with the thiol nucleophile glutathione
- ***Detoxication of Free Radicals***
  - Because O2 • can be converted into more reactive compounds , its elimination is an important detoxication mechanism
- This is carried out by superoxide dismutases (SOD)

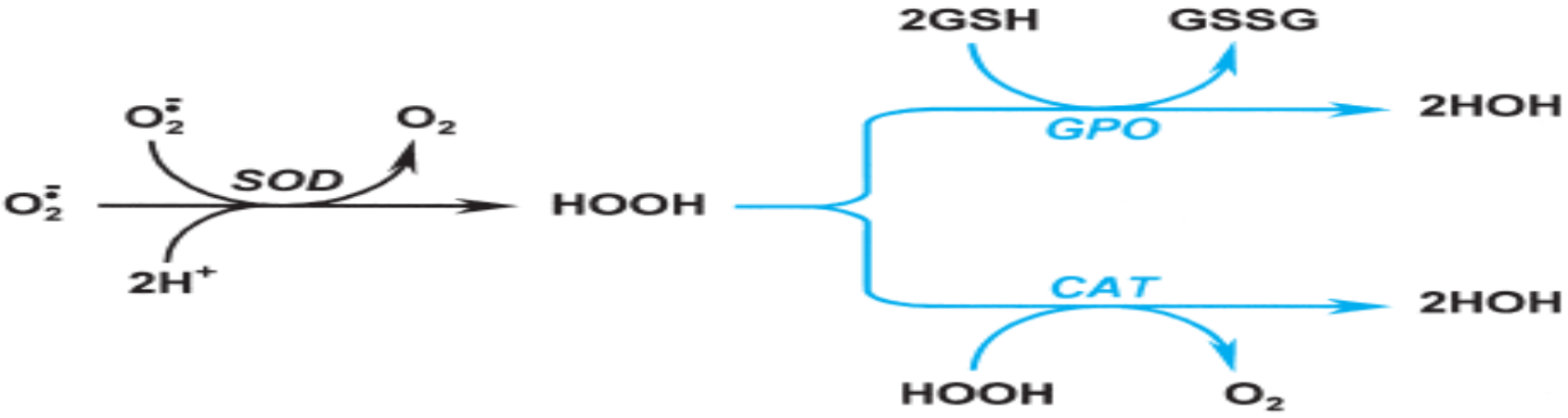



*Figure 3-5. Detoxication of superoxide anion radical ($O_2^{\cdot-}$) by superoxide dismutase (SOD), glutathione peroxidase (GPO), and catalase (CAT).*

# *THANK YOU!!!*